

What is claimed is:

1. A method of constructing a constrained helical peptide, comprising the steps of:

(a) synthesizing a peptide, wherein the peptide comprises a sequence of eight amino acid residues, wherein the sequence of eight amino acid residues has a first terminal residue and a second terminal residue, wherein the first terminal residue and the second terminal residue flank an internal sequence of six amino acid residues, and wherein the first and second terminal residues have a side chain containing an amide bond-forming substituent;

(b) providing a difunctional linker having a first functional group capable of forming an amide linkage with the side chain amide bond-forming substituent of the first terminal residue and having a second functional group capable of forming an amide linkage with the side chain amide bond-forming substituent of the second terminal residue; and

(c) cyclizing the peptide by reacting the side chain amide bond-forming substituent of the first terminal residue with the first functional group of the difunctional linker to form an amide linkage and reacting the side chain amide bond-forming substituent of the second terminal residue with the second functional group of the difunctional linker to form an amide linkage, yielding a constrained helical peptide.

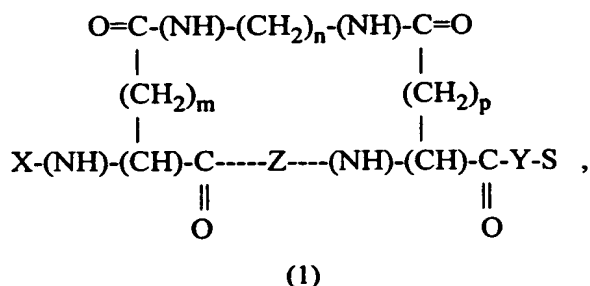
2. The method of claim 1 wherein in step (a) the side chain amide bond-forming substituent of the first terminal residue is protected with a first protecting group and the side chain amide bond-forming substituent of the second terminal residue is protected with a second protecting group, wherein the first protecting group and the second protecting group are differentially removable, and wherein in step (c) the first protecting group is removed such that the side chain amide bond-forming substituent of the first terminal residue is deprotected and the side chain amide bond-forming substituent of the second terminal residue is not deprotected before the peptide is reacted with the difunctional linker, and thereafter the peptide is reacted with the difunctional linker to form an amide linkage between the side chain amide bond-forming substituent of the first terminal residue and the first functional group of the difunctional linker, and thereafter the second protecting group is removed from the side chain amide bond-forming substituent of the second terminal residue and the peptide is cyclized by intramolecularly reacting the side chain amide bond-forming substituent of the second terminal residue with the second functional group of the difunctional linker to form an amide linkage.

3. A method of constructing a constrained helical peptide, comprising the steps of:

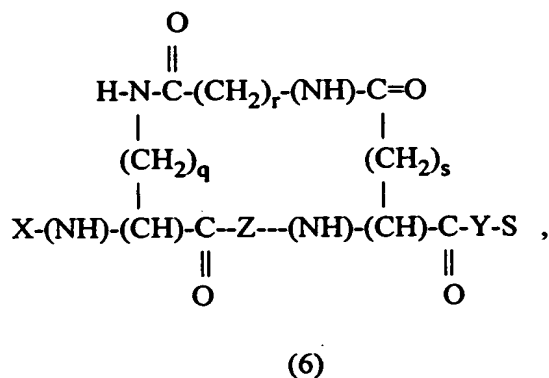
(a) synthesizing a peptide, wherein the peptide comprises a sequence of eight amino acid residues, wherein the sequence of eight amino acid residues has a first terminal residue and a second terminal residue, wherein the first terminal residue and the second terminal residue flank an internal sequence of six amino acid residues, wherein the first and second terminal residues have a side chain containing an amide bond-forming substituent, wherein the first terminal residue is coupled to a difunctional linker having a first functional group and a second functional group, wherein the first functional group is in an amide linkage with the side chain amide bond-forming substituent of the first terminal residue, and wherein the second functional group of the difunctional linker is capable of forming an amide linkage with the side chain amide bond-forming substituent of the second terminal residue; and

(b) cyclizing the peptide by intramolecularly reacting the side chain amide bond-forming substituent of the second terminal residue with the second functional group of the difunctional linker to form an amide linkage and yield a constrained helical peptide.

4. A compound selected from the group consisting of:
the compound represented by Formula (1):

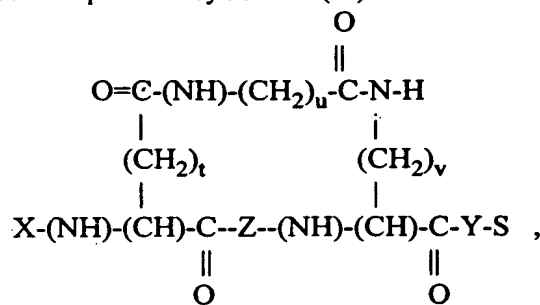


wherein S is absent or is a macromolecule, X is hydrogen or is any amino acid or amino acid sequence, Y is absent, or is hydroxyl if S is absent, or is any amino acid or amino acid sequence, Z is any amino acid sequence consisting of six amino acids; m and p are independently selected from the integers 0 to 6 inclusive, provided that m+p is less than or equal to 6, and n is any integer in the range defined by (7-(m+p)) to (9-(m+p)) inclusive, provided that n is greater than 1;
the compound represented by Formula (6):



wherein S is absent or is a macromolecule, X is hydrogen or is any amino acid or amino acid sequence, Y is absent, or is hydroxyl if S is absent, or is any amino acid or amino acid sequence, Z is any amino acid sequence consisting of six amino acids, q is selected from the integers 1 to 7 inclusive, s is selected from the integers 0 to 6 inclusive, provided that q+s is less than or equal to 7, and r is any integer in the range defined by (7-(q+s)) to (9-(q+s)) inclusive, provided that r is greater than 0;

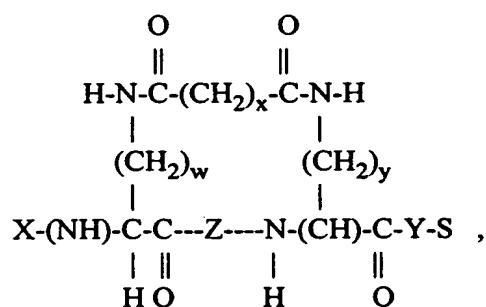
the compound represented by Formula (11):



(11)

wherein S is absent or is a macromolecule, X is hydrogen or is any amino acid or amino acid sequence, Y is absent, or is hydroxyl if S is absent, or is any amino acid or amino acid sequence, Z is any amino acid sequence consisting of six amino acids; t is selected from the integers 0 to 6 inclusive, and v is selected from the integers 1 to 7 inclusive, provided that t+v is less than or equal to 7; and u is any integer in the range defined by (7-(t+v)) to (9-(t+v)) inclusive, provided that u is greater than 0; and

the compound represented by Formula (16):



(16)

wherein S is absent or is a macromolecule, X is hydrogen or is any amino acid or amino acid sequence, Y is absent, or is hydroxyl if S is absent, or is any amino acid or amino acid sequence, Z is any amino acid sequence consisting of six amino acids; w and y are independently selected from the integers 1 to 7 inclusive, provided that w+y is less than or equal to 8, and x is any

integer in the range defined by $(7-(w+y))$ to $(9-(w+y))$ inclusive, provided that x is greater than or equal to 0.

5. The compound of claim 4 that is the compound of Formula (1), wherein Z is Gln-Gln-Arg-Arg-Phe-Tyr.
- 5 6. A constrained helical peptide made according to the method of claim 1.
7. A constrained helical peptide made according to the method of claim 3.
8. A compound according to claim 4, wherein Z is an amino acid sequence consisting of six amino acids, wherein the internal sequence of six amino acids has the form **gabcde**, **defgab**, or **cdefga** and is selected from the group of sequences consisting of a sequence of six contiguous amino acids in HIV-1LAI strain gp41 amino acid sequence 633 to 678, in its homolog sequence from another HIV strain, in a consensus sequence of its homolog sequences from any one HIV clade, or amino acid substituted variant thereof, in which amino acid 633 or its corresponding amino acid in the homolog, consensus or variant sequence is assigned position **a** of a repeating **abcdefg** assignment.
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- 15 9. The compound of claim 8, further comprising S' when S is absent and X is any amino acid or amino acid sequence, wherein S' is a macromolecule attached to X.
10. A compound comprising a first constrained helical peptide comprising a peptide comprising a sequence of eight amino acid residues, wherein the sequence of eight amino acid residues has a first terminal residue and a second terminal residue, wherein the first terminal residue and the second terminal residue flank an internal sequence of six amino acids, wherein the first and second terminal residues have a side chain that are linked to each other forming a locking moiety to form a constrained helical peptide, wherein the internal sequence of six amino acids has the form **gabcde**, **defgab**, or **cdefga** and is selected from the group of sequences consisting of a sequence of six contiguous amino acids in HIV-1LAI strain gp41 amino acid sequence 633 to 678, in its homolog sequence from another HIV strain, in a consensus sequence of its homolog sequences from any one HIV clade, or in an amino acid substituted variant thereof, in which amino acid 633 or its corresponding amino acid in the homolog, consensus or variant sequence is assigned position **a** of a repeating **abcdefg** assignment.
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- 30 11. The compound of claims 8 or 10, wherein the homolog or consensus sequence is shown in Figures 16A-16G.

12. A compound of claims 8 or 10, further comprising a second constrained helical peptide.
13. An antibody that binds to a compound of claim 8, wherein the antibody specifically binds an epitope comprising an amino acid at position a, d, e, or g in the helical peptide.
14. A method to prophylactically or therapeutically treat a mammal at risk for or infected with HIV,
5 comprising administering a prophylactically or therapeutically effective amount of a compound of claims 8 or 10.
15. The method of claim 14, wherein the composition comprises internal six amino acid sequences from different HIV strains or HIV clades.
16. A vaccine comprising at least one compound of claims 8 or 10.

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